09-10-02

Attorney Docket No. 80505

DAG

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re patent of: Caput et al.

Patent No.: 5,382,518

Granted: January 17, 1995

Serial No. 920,519

Filing Date: April 25, 1991

For: URATE OXIDASE ACTIVITY PROTEIN, RECOMBINANT GENE CODING THEREFORE, EXPRESSION VECTOR, MICRO-ORGANISMS AND TRANSFORMED CELLS

CERTIFICATE UNDER 37 C.F.R. 1.10(b)

Express Mail Label Number: EL676470164US

Date of Deposit: September 9, 2002

I hereby certify that this paper is being deposited with the United Stated Postal Service "Express Mail Post Office to Addressee" Service on the indicated above and is addressed to: Commissioner for Patents, Box Patent Extension, Washington, DC 20231

Name

9/9/02

Date

Commissioner for Patents
Box Patent Extension
Washington, D.C. 20231

Dear Sir:

TRANSMITTAL LETTER FOR APPLICATION FOR EXTENSION OF PATENT TERM UNDER 35 U.S.C. §156 and 37 C.F.R. §1.740

Submitted herewith in triplicate is an application for extension of patent term of the above-identified patent pursuant to 35 U.S.C. §156 and 37 C.F.R. §1.740.

The Commissioner is hereby authorized to charge the fee of $1,120 under 37 C.F.R.§1.20(j) and any other fee which may be required for receiving and acting upon the accompanying application for extension to Deposit Account No. 19-0091. A duplicate copy of this letter is enclosed.

Respectfully submitted,

Michael D. Alexander September 9, 2002

Michael D. Alexander
Registration No. 36,080

09/12/2002 BNGUYEN1 00000002 5382518
01 FC:111 1120.00 CH

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re patent of: Caput et al.

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Date 9/9/02

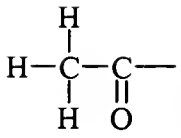
Commissioner for Patents
Box Patent Extension
Washington, D.C. 20231

APPLICATION FOR EXTENSION OF PATENT TERM UNDER 35 U.S.C. §156 AND 37 C.F.R. §1.740

Dear Sir:

Under the provisions of 35 U.S.C. §156 and in accordance with 37 C.F.R. §1.740, Sanofi-Synthelabo, the owner of the entire right, title and interest in United States Patent No. 5,382,518 which claims rasburicase, hereby requests that the term of said patent, originally expiring on January 17, 2012, be extended 1,638 days to expire on July 12, 2016. The chain of title of United States Patent No. 5,382,518 from the inventors to Sanofi-Synthelabo is attached hereto as Exhibit 1.

(1) Rasburicase is the generic name of a recombinant urate-oxidase enzyme produced by a genetically modified *saccharomyces cerevisiae* strain. The cDNA coding for rasburicase was cloned from a strain of *Aspergillus flavus*. Rasburicase is a tetrameric protein with identical subunits of a molecular mass of 34151.65 daltons (monomer). The molecular formula of the monomer is $C_{1523}H_{2383}N_{417}O_{462}S_7$. The monomer, made up of a single 301 amino acid polypeptide chain, has no intra or inter-disulfide bridges, is N-terminal acetylated, and has the structural formula:



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SAVKAARYGK DNVRVYKVHK DEKTGVQTVY EMTVCVLLEG EIETSYTKAD  50
NSVIVATDSI KNTIYITAKQ NPVTPPELFG SILGTHFIEK YNHIHAAHVN 100
IVCHRWTRMD IDGKPHPHSF IRDSEEKRNV QVDVVEGKGI DIKSSLSGLT 150
VLKSTNSQFW GFLRDEYTTL KETWDRILST DVDATWQWKN FSGLQEVRSH 200
VPKFDATWAT AREVTLKTFA EDNSASVQAT MYKMAEQILA RQQLIETVEY 250
SLPNKHYFEI DLSWHKGLQN TGKNAEVFAP QSDPNGLIKC TVGRSSLKSK 300
L                                                       301
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K : lysine residue                A : alanine residue
F : phenylalanine residue         M : methionine residue
P : proline residue               H : histidine residue
T : threonine residue             Q : glutamine residue
I : isoleucine residue            E : glutamic acid residue
L : leucine residue               Y : tyrosine residue
S : serine residue                C : cysteine residue
R : arginine residue              W : tryptophane residue
D : aspartic acid residue         V : valine residue
N : asparagine residue            G : glycine residue
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(2) Rasburicase was subject to regulatory review by the Food and Drug Administration (FDA) under Section 351 of the Public Health Service Act.

(3) Rasburicase, having the tradename, ELITEK™, was approved for commercial marketing or use by the Food and Drug Administration under Section 351 of the Public Health Service Act on July 12, 2002.

(4) The active ingredient in the approved product is rasburicase. Rasburicase has not been previously approved for commercial marketing or use under the Public Health Service Act.

(5) This application is being submitted within the sixty-day period permitted for submission pursuant to 37 C.F.R. §1.720(f). The last day on which this application can be submitted is September 10, 2002.

(6) The patent for which an extension is being sought is United States Patent No. 5,382,518, issued January 17, 1995 in the name of Daniel Caput, Pascual Ferrara, Jean-Claude Guillemot, Mourad Kaghad, Richard Legoux, Gérard Loison, Elisabeth Larbre, Johannes Lupker, Pascal Leplatois, Marc Salome and Patrick Laurent and having an expiration date of January 17, 2012.

(7) A complete copy of United States Patent No. 5,382,518, including the entire specification, claims, and drawings, is attached hereto as Exhibit 2.

(8) Copies of the following documents in United States Patent No. 5,382,518 are attached hereto as Exhibit 3:

The Maintenance Fee Record and the Maintenance Fee Statements showing payment of the 4th, and 8th year maintenance fees.

No disclaimer, certificate of correction or reexamination certificate has been issued in this patent.

(9) United States Patent No. 5,382,518 claims the product rasburicase (claims 1-6 and 8-9) and a pharmaceutical composition comprising rasburicase (claim 7). A demonstration of how claims 7 and 8 read on the approved product is set forth below:

> Claim 7 reads on a pharmaceutical composition comprising a protein according to claim 1. Claim 1, in turn, is directed to the 301 amino acid polypeptide chain of rasburicase.
>
> Claim 8 reads on the N-terminal acetylated 301 amino acid polypeptide chain of rasburicase.

10.) Rasburicase was subject to a regulatory review period consisting of (a) the period from January 27, 1996, the effective date of Investigational New Drug (IND) Application No. 49,626 submitted December 28, 1995 under Section 505(i) of the Federal Food, Drug and Cosmetic Act (on September 21, 1999 the responsibility for the regulatory review of this product was moved from CDER to CBER and a new IND number, BB-IND8688, was issued on November 15, 1999) to December 16, 1999, the initial submission date of the Biologics License Application (BLA) No. BLA-991470 (was subsequently changed to BL103946-0) under Section 351 of the Public Health Service Act and (b) the period from December 16, 1999, the initial submission date of the BLA to July 12, 2002, the date of approval of the BLA.

(11) The significant activities undertaken by or on behalf of applicant and responses by the FDA during the applicable review period with respect to the approved product are as follows:

SUMMARY OF ELITEK™ (rasburicase)
IND AND NDA ACTIVITIES

Date	Activity
June 16, 1995	Submitted a request for a Pre-IND and End-of-Phase II meeting and an initial pre-meeting background package.
October 31, 1995	Submitted Pre-IND and End-of-Phase II Meeting pre-meeting package.
December 19, 1995	Pre-IND and End-of-Phase II Meeting with FDA
December 27, 1995	Final Minutes from Pre-IND and End-of-Phase II Meeting establishing agreements for development for approval with CDER's Oncology Division.
December 28, 1995	Submission of IND application for rasburicase (SR29142)
January 11, 1996	FDA acknowledgment of receipt of IND; assignment of IND number 49,626
January 27, 1996	Effective date of IND
September 6, 1996	Submitted randomized clinical protocol LTS3025
February 17, 1999	Submitted request for a pre-NDA CMC meeting
March 12, 1999	Submitted pre-meeting package for pre-NDA CMC meeting
April 8, 1999	Submitted request for pre-NDA Clinical meeting
April 13, 1999	Pre-NDA CMC meeting with CDER's Oncology Division
April 15, 1999	Submitted minutes to FDA for April 13, 1999 pre-NDA CMC Meeting.
May 25, 1999	Submitted pre-meeting package for pre-NDA Clinical meeting
June 10, 1999	Pre-NDA Clinical meeting with CDER's Oncology Division
June 23, 1999	Submitted minutes to FDA for June 10, 1999 pre-NDA Clinical meeting with CDER's Oncology Division
September 17, 1999	Received fax from FDA changing jurisdiction from CDER to CBER for IND. This changes NDA to a BLA submission.
September 21, 1999	CDER's Oncology Division meets with CBER to discuss jurisdiction change and agreed to change.
October 26, 1999	Submitted request for 2 pre-BLA meetings; one for CMC and other for Clinical.

October 27, 1999	CBER request an informal submission of IND 49,626 documents to assist in transfer of IND from CDER to CBER
November 3, 1999	Received fax from CBER scheduling pre-BLA Clinical meeting for December 9, 1999.
November 3, 1999	Submitted copies of CBER's requested documents from IND 49,626 as requested on October 27, 1999.
November 3, 1999	Contacted CBER's electronic submission coordinator, Michael Fauntleroy
November 9, 1999	Received fax from CBER scheduling the pre-BLA CMC meeting for December 8, 1999.
November 5, 1999	Submitted request for a pre-BLA meeting to review computer-assisted license applications (CALA) components.
November 9, 1999	Submitted pre-meeting package for pre-BLA CMC meeting scheduled for December 8, 1999 with CBER.
November 10, 1999	Teleconference with CBER's Joe Montgomery regarding electronic submissions.
November 10, 1999	Teleconference with CBER's Joe Montgomery for follow-up information on electronic submissions.
November 15, 1999	Submitted via fax questions regarding CBER's electronic submissions to Michael Fauntleroy
November 15, 1999	Submitted pre-meeting package for the pre-BLA Clinical meeting scheduled for December 9, 1999.
November 10, 1999	Received acknowledgement letter of transfer of IND49,626 from CDER to CBER and assignment of BB-IND #8688
November 15, 1999	CBER's Michael Fauntleroy provided some responses to questions regarding electronic submission of BLA as a CALA.
November 23, 1999	Submitted demonstration CD-ROM of CALA with reminder of November 5, 1999 request for a meeting.
December 8, 1999	Submitted request for brandname evaluation by CBER.
December 3, 1999	Submitted two orphan drug applications to Office of Orphan Products Development, FDA. One for treatment of hyperurceima and other for prophylaxis of hyperuricemia.
December 8, 1999	Pre-BLA CMC meeting held with CBER
December 9, 1999	Pre-BLA Clinical meeting held with CBER
December 13, 1999	Received two letters from Office of Orphan Product Development acknowledging receipt of the applications submitted on December 3, 1999, with assignment of Application #99-1314 and 99-1315.

December 13, 1999	Submitted pre-BLA CMC meeting minutes to CBER
December 13, 1999	Submitted pre-BLA Clinical meeting minutes to CBER
December 16, 1999	Submitted via fax an advanced copy of BLA overall Table of Contents as requested by CBER at pre-BLA Clinical meeting.
December 16, 1999	Submitted BLA containing 173 volumes to CBER. BLA assigned Number BLA-991470
December 18, 1999	Receive letter from CBER with reminder of requirement that as of April 1, 1999 all applications must contain assessment information in pediatrics or a request for waiver must be submitted and granted.
February 2, 1999	Received copies of CBER's version of the final minutes for pre-BLA CMC and Clinical meetings held on December 8 +9, 1999, respectively.
February 8, 1999	Received letter from CBER acknowledging initial review completed for filing of BLA application. Application under active review by CBER.
February 10, 1999	Submitted production schedule to FDA for manufacturing of rasburicase to schedule pre-approval inspections.
March 6, 2000	Received two letters from Office of Orphan Drug Products requesting revised estimates of prevalence estimates for two orphan applications submitted December 3, 1999 (Application #99-1314 and 99-1315)
April 13, 2000	Submitted 120 Day Safety up-date.
April 19, 2000	Received letter from CBER regarding guidance document on FDA's revised position on BSE requirements.
June 29, 2000	Submitted responses to Office of Orphan Drug Products Development in response to their letters of March 6, 2000 (Application # 99-1314 and 99-1315).
July 18, 2000	Amended BLA to provide draft mechanicals of container labeling/carton label mock-ups.
August 18, 2000	Amended BLA for CMC to correct an error regarding siliconization of stoppers.
September 7, 2000	CBER requested copies of development reports for ELISA IgG assay and neutralizing antibody assessment assay.
September 8, 2000	Amended BLA to provide CBER with requested development reports for ELISA IgG assay and neutralizing antibody assessment assay.
September 27, 2000	CBER requested information on calculation method of dosing parameters.

October 3, 2000	Amended BLA responding to FDA's September 27, 2000 request for information on calculation method of dosing parameters.
October 11, 2000	Received notification from Office of Orphan Products that orphan designation for rasburicase was granted for treatment of hyperuricemia (Application #99-1314) and prophylaxis of hyperuricemia (Application #99-1315)
November 3, 2000	Submitted copies of Office of Orphan Products Development letters designating rasburicase as an orphan product for requested indications to CBER.
November 6, 2000	Received BLA Action Letter from CBER stating that BLA data was inadequate for approval with outline of deficiencies that needed to be addressed for approval. The review clock was stopped as of this date.
November 10, 2000	Teleconference with medical reviewer to clarify FDA questions 32 , 36, +38 from November 6, 2000 letter.
November 13, 2000	Teleconference with medical reviewer for FDA to provide agreement on approach to response to questions 32, 26, and 38.
November 15, 2000	Submitted response to FDA's Full Response letter dated November 6, 2000 noting Sanofi-Synthelabo's intent to file an amendment to address FDA's questions/concerns outlined in the FDA's letter.
November 20, 2000	Teleconference with FDA's CMC reviewer to discuss questions 1,4,5 and 7.
November 28, 2000	FDA left a voicemail regarding FDA's position that it was too early to discuss CMC post-marketing commitments.
February 2, 2001	Teleconference with FDA's CMC reviewer to discuss FDA's CMC question 1. FDA agreed with proposed approach for response and agreed to timing as post-marketing commitment.
February 27, 2001	Submitted full response to BLA Action Letter dated November 6, 2000.
March 6, 2001	Received letter from acknowledging receipt of February 28, 2001 submission and designation as a Class 2 submission with a BLA action date of August 30, 2001.
March 28, 2001	Submitted a request for a Type A meeting regarding the BLA review and the Class 2 submission designation.
April 2, 2001	FDA requested submission of post-marketing commitments and an electronic copy of the proposed package insert with line numbering.
April 9, 2001	Submitted electronic copy of proposed package insert with line numbering.

April 9, 2001	Submitted withdrawal of request for a Type A meeting submitted on March 28, 2001 based on information from FDA that CBER was moving toward final approval. Sanofi-Synthelabo acknowledged teleconference scheduled for May 1, 2001 to discuss final review process.
May 1, 2001	Teleconference to discuss review process, with FDA stating that all responses submitted on February 27, 2001 addressed FDA's questions for review by August 30, 2001 as outlined in FDA's letter.
May 4, 2001	Received fax from FDA's project manager providing agreement on tradename (Elitek), vial, carton and solvent labeling. FDA requested submission of Phase IV protocols for post-marketing commitments to review.
June 14, 2001	Teleconference with FDA requesting additional information by submitted to support the February 27, 2001 amendment.
June 25, 2001	Submitted color mock-ups of container/carton labeling revised based on comments from FDA's May 4, 2001 fax.
June 25, 2001	Submitted information on allergic reactions recently received.
July 10, 2001	Teleconference with FDA's CMC reviewer requesting a feedback meeting/teleconference.
July 19, 2001	Teleconference with FDA's CMC reviewer agreeing to responses for questions 1-26 with pending questions from Questions 1,4,7, and 10.
July 20, 2001	Submitted full response to June 14, 2001 teleconference request
July 20, 2001	FDA's medical reviewer called with a request for additional information.
July 20, 2001	Submitted response to FDA questions for questions 1,4,7 and 10 as requested during the July 19, 2001 teleconference with FDA.
July 24, 2001	Submitted response to FDA's questions received via telephone on July 20, 2001 from FDA's medical reviewer
August 16, 2001	FDA faxed proposed revisions to package insert.
August 30, 2001	Received FDA's BLA Action Letter stating BLA is inadequate to support final approval, which included additional new questions. BLA review clocked stopped.
September 7, 2001	Submitted response to FDA's request for information outlined in FDA's August 16, 2001 fax.
September 10, 2001	Submitted a complete response to FDA's August 20, 2001 BLA Action Letter.

September 18, 2001	Submitted additional information to address FDA's August 20, 2001 BLA Action Letter.
September 21, 2001	FDA's project manager called to request submission of 3 copies of datasets submitted in the original BLA submission on CD-Rom.
September 24, 2001	Submitted 3 copies of datasets from original BLA on CD-Rom as requested by FDA's project manager on September 21, 2001.
October 2, 2001	Submitted via fax a request for a Type A meeting to review expectations for finalization of BLA review that would lead to a timely approval.
October 26, 2001	Received letter stating that Sanofi-Synthelabo's response to the FDA's August 20, 2001 letter were not considered complete, since there were some changes in the FDA's letter that were different from that communicated during teleconferences and the letter's request take precedent.
January 3, 2002	Teleconference with FDA's immunogenicity reviewer to discuss FDA's current position on immunogenicity requirements.
January 8, 2002	Submitted full response to FDA's October 26, 2001 BLA Action Letter.
February 4, 2002	Received letter from FDA acknowledging receipt of January 8, 2002 submission, with a Class 2 response assignment. FDA's BLA action date is July 12, 2002.
March 4, 2002	Teleconference with FDA's medical reviewer requesting revised AE database from compassionate use studies LTS3256 and LTS3257.
March 7, 2002	Submitted requested AE databases requested on March 4, 2002.
March 13, 2002	Submitted two invitro studies requested be conducted by FDA in FDA's November 6, 2000 letter as post-marketing commitment studies.
March 20, 2002	FDA's medical reviewer called with additional questions.
March 25, 2002	Submitted response to FDA's questions received on March 20, 2002.
March 25, 2002	Telephone request from FDA requesting resubmission of tradename, Elitek for review again.
March 28, 2002	Received fax from FDA with agenda for a teleconference on April 8, 2002.
March 29, 2002	Submitted request for brandname, Elitek review as requested on March 25, 2002.

April 1, 2002	Submitted additional response to FDA's request for information made on March 20, 2002.
April 2, 2002	Submitted another copy of DOH0172 as requested by FDA.
April 8, 2002	Submitted response to FDA's Emailed question dated March 26, 2002.
April 25, 2002	FDA's project manager called regarding comments on package insert.
May 6, 2002	Received fax from FDA outlining immunogenicity post-marketing commitments.
June 4, 2002	Teleconference to discuss FDA's comments on package insert.
June 5, 2002	Submitted response to FDA's comments at June 4 package insert teleconference.
June 5, 2002	Received fax from FDA with questions from FDA's medical reviewer.
June 11, 2002	Submitted sample vial labeled for review.
June 17, 2002	Submitted response to June 5, 2002 package insert teleconference.
June 18, 2002	Submitted response to FDA's June 5, 2002 questions from medical reviewer.
June 18, 2002	Submitted a complete listing of post-marketing commitments.
June 21, 2002	Received fax comments from FDA on package insert.
July 2, 2002	Received fax comments from FDA on package insert.
July 2, 2002	Submitted final vial, ampule and carton labels as color mock-ups.
July 3, 2002	Submitted revised package insert.
July 9, 2002	Teleconference to discuss package insert.
July 9, 2002	Submitted revised package insert.
July 9, 2002	Received fax from FDA with final drafts of post-marketing commitments.
July 10, 2002	Teleconference to discuss package insert.
July 10, 2002	Submitted revised package insert.
July 11, 2002	Teleconference to discuss package insert and post-marketing commitments.
July 11, 2002	Submitted final revised package insert and post-marketing commitments.
July 12, 2002	Teleconference to discuss revisions to post-marketing commitments.

July 12, 2002	Submitted final post-marketing commitments agreed to with FDA.
July 12, 2002	Received FDA's BLA Action Letter granting approval
August 27, 2002	Submitted Final Printed Labeling

(12) In the opinion of the Applicant, U.S. Patent No. 5,382,518 is eligible for an extension of 1,638 days. The length of said extension was calculated as follows:

1.	The number of days for the testing phase as defined in 37 CFR 1.775 (c)(1)	1,419
2	The number of days for the approval phase as defined in 37 CFR 1.775(c)(2)	940
3	Total of line 1 and 2	2,359
4.	The number of days of the period of line 2 which occurred prior to the issue date of the patent	0
5.	The number of days of the period of line 2 during which the Applicant failed to act with due diligence as defined in 37 CFR 1.775(d)(1)(ii)	0
6.	Total of line 4 and line 5	0
7.	Total of line 3 less the amount of line 6	2,359
8.	The number of days of the period of line 1 which occurred prior to the issue date of the patent	0
9.	The number of days of the period of line 1 during which the Applicant failed to act with due diligence as defined in 37 CFR 1.775(d)(1)(ii)	0
10.	The total of line 8 and line 9	0
11.	Total of line 7 less the amount of line 10	2,359
12.	The number of days from line 1	1,419
13.	The number of days from line 10	0
14.	The total of line 12 less the amount of line 13	1,419
15.	One half of line 14	709.5
16.	The total of line 11 less the amount of line 15	1,649.5
17.	The original expiration date of the patent	January 17, 2012
18.	The expiration date of the patent if extended by the number of days on line 16	July 24, 2016

19.	Date of the FDA final approval	July 12, 2002
20.	Limitation set forth in 37 CFR 1.775(d)(3)	14 years
21.	14 years added to the date on line 19 gives a revised date of	July 12, 2016
22.	Earlier of the dates of line 18 or line 21	July 12, 2016
23.	Original expiration date of patent	January 17, 2012
24.	The patent issued after 09/24/84	5 years
25.	The number of years on line 24 added to the date on line 23	January 17, 2017
26	The earlier of the dates appearing on line 22 or line 25	July 12, 2016
27.	The original expiration date of the patent	January 17, 2012
28.	The number of days by which line 26 and line 27 differ	1,638

(13) Sanofi-Synthelabo acknowledges its duty to disclose to the Commissioner for Patents and the Secretary of Health and Human Services any information of which it is aware which is material to the determination of entitlement to the extension sought.

(14) The Commissioner is hereby authorized to charge to Deposit Account No. 19-0091 the prescribed fee of $1,120 under 37 C.F.R. §1.20(j), and to charge any additional fees which may be required, or credit any overpayment to said Deposit Account.

(15) Correspondence relating to this application should be directed to:

Michael D. Alexander
Sanofi–Synthelabo Inc.
9 Great Valley Parkway
Malvern, PA 19355

Telephone or facsimile communications relating to this application can be directed to the undersigned at the numbers listed below.

Respectfully submitted,

Dated: September 9, 2002

Michael D. Alexander
Attorney for Applicant
Registration No. 36,080

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